REMARKS

Applicants acknowledge with appreciation the Examiner's indication that the full length sequence of SEQ ID NO.: 1 with an insert between amino acid residues 248 and 267 or between amino acid residues 251 and 252 is free of the prior art.

Amendments to the Specification

The Examiner has maintained an objection to the specification for containing a figure in the abstract.

Applicants had previously amended the abstract to remove the figure, as submitted on page 10 of the November 4, 2009 AMENDMENT AND REPLY TO OFFICE ACTION. However, applicants note that, pursuant to 37 C.F.R. § 1.72(b), amendments to the abstract must be set forth on a separate sheet. Pursuant to 37 C.F.R. § 1.121, the amendment must also show all changes relative to the previous version. Applicants have therefore resubmitted a marked-up copy of the amendment to the abstract above in which the figure is deleted. The word "therapeutic" has also been added to the abstract. Support for this amendment can be found throughout the application as originally filed, e.g., at page 1, line 6; page 4, line 17; and page 9, line 20. Accordingly, applicants respectfully request that the Examiner withdraw the objection.

Amendments to the Claims

Claims 1, 4, 5, 8, 9, 11-15, 30 and 31 have been amended. Claims 8-35 had previously been withdrawn. Claim 6 had previously been canceled. Claim 36 has been introduced. Thus, claims 1-5 and 7-36 are pending in this application following entry of these amendments.

Applicants have amended claim 1 to specify that the insert of each protein species is a polypeptide of varying amino acid sequence, and that the library comprises at least

two different protein species. Support for this amendment can be found throughout the application as originally filed, e.g., at page 2, lines 24 to 29; and page 6, lines 1 to 11. Applicants have also amended claim 1 to improve its form by deleting "into which an insert has been introduced" in the third line of the claim. Applicants have further amended claim 1 to provide proper antecedent basis by replacing "the insert" in line 5 with "an insert."

Applicants have amended claim 4 to specify that the protein species of the library comprise A1 domain sequences selected from amino acid residues 7 to 257 of SEQ ID NO.: 1, and a protease-sensitive sequence C-terminal to the A1 domain sequences into which an insert may be introduced without abolishing catalytic activity of A1 domain sequences. Support for this amendment can be found in the application as originally filed, e.g., at page 7, lines 19 to 23; and Figure 1.

Applicants have amended claim 5 to improve its form, and have replaced "SEQ ID No.: 1" with "SEQ ID NO.: 1" for consistency.

Applicants have amended claim 8 to specify that the insert of each protein species is a polypeptide of varying amino acid sequence, and that the library comprises at least two different members. Support for this amendment can be found throughout the application as originally filed, e.g., at page 2, lines 24 to 29; page 3, lines 7 to 11; page 6, lines 1 to 11; and page 11, lines 4 to 10. Applicants have also amended claim 8 to improve its form by deleting "into which an insert has been introduced" in the third line of the claim. Applicants have further amended claim 8 to provide proper antecedent basis by replacing "the insert" in line 5 with "an insert." Applicants have also amended claim 8 to replace "SEQ ID No.: 1" with "SEQ ID NO.: 1" for consistency.

Applicants have amended claim 9 to specify that the insert of the protein is a polypeptide of varying amino acid sequence. Support for this amendment can be found throughout the application as originally filed, e.g., at page 2, lines 24 to 29. Applicants have also amended claim 9 to improve its form by deleting "into which an insert has been

introduced" in the third line of the claim. Applicants have further amended claim 9 to provide proper antecedent basis by replacing "the insert" in line 5 with "an insert." Applicants have also amended claim 8 to replace "SEQ ID No.: 1" with "SEQ ID NO.: 1" for consistency.

Applicants have amended claim 11 to specify that the sequence of the mutant protein is selected from SEQ ID NO.: 1. Support for this amendment can be found in the application as originally filed, e.g., page 3, lines 2 to 5; SEQ ID NO.: 1, line <223>. Applicants have also amended claim 8 to replace "SEQ ID No.: 1" with "SEQ ID NO.: 1" for consistency.

Applicants have amended claim 12 to improve its form, and to replace "SEQ ID No.: 1" with "SEQ ID NO.: 1" for consistency.

Applicants have amended claim 13 to replace "SEQ ID No.: 6" with "SEQ ID NO.: 6" for consistency.

Applicants have amended claim 14 to replace "SEQ ID No.: 7" with "SEQ ID NO.: 7" for consistency.

Applicants have amended claim 15 to replace "SEQ ID No.: 1" with "SEQ ID NO.: 1" for consistency.

Applicants have amended claim 30 to specify that the protein sequences encoded by the DNA members of the library are selected from SEQ ID NO.: 1. Support for this amendment can be found in the application as originally filed, e.g., page 3, lines 2 to 5; SEQ ID NO.: 1, line <223>.

Applicants have amended claim 31 to improve its form.

Applicants have introduced claim 36 to recite combinatorial protein libraries with inserts between amino acids 248 and 267 of SEQ ID NO.: 1. Support for this amendment

can be found in the application as originally filed, e.g., page 6, line 29 to page 7, line 2; Figures 1, 4, and 5

None of these amendments introduces any new matter.

THE REJECTIONS

35 U.S.C. § 112, second paragraph

Claims 4 and 5

The Examiner has maintained the rejection of claims 4 and 5 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Specifically, the Examiner states that it is unclear how much of SEQ ID NO.: 1 is required for catalytic activity and how much of the A2 domain is required to introduce the insert. Applicants traverse in view of the claim amendments made herein.

Amended claim 4 specifies that the protein species comprise A1 domain sequences selected from SEQ ID NO.: 1 sufficient to retain A1 domain catalytic activity and protease-sensitive sequences introduced C-terminal to the A1 domain sequences that do not abolish A1 domain catalytic activity. It was well within the skill in the art at the effective filing date to perform deletion, insertion, and substitution analyses which monitor the loss of activity, as shown, for example, by Yamamoto et al. (Yamamoto et al., "Mutational and comparative analysis of Streptolysin O, an oxygen-labile Streptococcal hemolysin," *Biosci Biotechnol Biochem* 65:2682-2689 (2001)). Therefore, it was also well within the skill of the art at the effective filing date to test how much of SEQ ID NO.: 1 is required for catalytic activity. For loss of activity in SLT-1, see, for example, LaPointe et al. (LaPointe et al., "A role for the protease-sensitive loop region of Shiga-like Toxin 1 in the retrotranslocation of its A_1 domain from the endoplasmic reticulum lumen," *J Biol Chem* 280:23310-23318 (2005)). Because one of skill in the art could easily test whether a protein comprising a sequence selected from SEQ ID NO.: 1 has catalytic activity, proteins with inserts could likewise easily be tested for the

retention or abolishment of catalytic activity. Thus, amended claim 4 is clear. Because amended claim 5 depends from amended claim 4, and thus, includes all the limitations of amended claim 4, it is also clear. Accordingly, applicants request that the Examiner withdraw the rejection.

Provisional obviousness-type double patenting

Claims 1-5 and 7

The Examiner has maintained the provisional rejection of claims 1-5 and 7 under the judicially-created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 129-145 of co-pending U.S. Patent Application 12/088,206 ("the '206 application").

Applicants respectfully submit that the provisional rejection of claims 1-5 and 7 of the instant application is premature and unfairly prejudiced to applicants because the final form of the allowed claims in both the instant application and the '206 application cannot be determined at this time. Applicants maintain their request that this provisional rejection be held in abeyance until the claims of this application or the '206 application are found allowable. At that time, applicants will consider filing a Terminal Disclaimer as is appropriate and proper.

35 U.S.C. § 102(b)

Claims 1-3 and 7

The Examiner has rejected claims 1-3 and 7 under 35 U.S.C. § 102(b) over U.S. Patent Publication US2002/0094334 ("Keener"). Specifically, the Examiner states that "Keener et al. teach variants of AB toxins wherein an insert is present in the protease-sensitive loop" (Office Action, page 8). Applicants respectfully traverse.

In contrast to the Examiner's characterization of Keener that it discloses ***variants of AB toxins***, amended claim 1 of the instant application (and therefore, claims that depend

therefrom) is directed to ***combinatorial protein libraries*** comprising a plurality of different ABx toxin species. Keener does not teach or suggest combinatorial protein libraries, as recited in the claimed invention.

Furthermore, the Examiner has mischaracterized Keener as teaching inserts in a protease-sensitive loop of an A chain, including inserts that are 12 amino acids long. Instead, Keener discloses ***substitution*** mutations in a ***native*** (i.e., pre-existing) linker ***between the A and B chains of a toxic protein***, wherein the native linker is 12 amino acids long, and the first 10 amino acids of the linker are ***substituted*** so as to modify protease specificity. By contrast, amended claim 1 of the instant application recites ***inserts*** into a protease-sensitive loop in the A chain that comprise at least 2 amino acid residues. Thus, the described ***substitution*** in Keener is not the same as the ***insertion*** recited in the claimed invention.

For at least the above reasons, amended claim 1 (and thus, claims dependent therefrom) are patentable over Keener and applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 102(e)

Claims 1-2 and 7

The Examiner has rejected claims 1-2 and 7 under 35 U.S.C. § 102(e) over U.S. Patent 7,375,186 ("Borgford"). Specifically, the Examiner states that "Borgford teaches libraries of AB toxins wherein an insert is introduced into the protease-sensitive region " (Office Action, page 9). Applicants respectfully traverse.

Amended claim 1 of the instant application (and therefore, claims that depend therefrom) recites a ***combinatorial protein library*** comprising a plurality of ABx toxic proteins. Borgford does not teach or suggest combinatorial protein libraries. Instead, Borgford refers to individual AB toxin species, but nowhere does it teach or suggest a combinatorial protein library of these toxins.

For at least the above reasons, amended claim 1 (and thus, claims dependent therefrom) are novel over Borgford and applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 103

Claims 1-5 and 7

The Examiner has rejected claims 1-5 and 7 under 35 U.S.C. § 103 over the combination of Keener and WO 99/40185 ("Gariepy"). Specifically, the Examiner states that Keener teaches variants of AB toxins but does not teach a library comprising a known size of protein species. The Examiner also states that Gariepy teaches polypeptide libraries of a known size comprising Shiga-like toxin A chains (SEQ ID NO.: 1). The Examiner therefore concludes that it would have been obvious to substitute Keener's library of unknown size with Gariepy's library of specific size comprising Shiga-like toxins. Applicants respectfully traverse.

As discussed above, Keener neither teaches nor suggests combinatorial protein libraries. Therefore, there would be no motivation for one of skill in the art to combine references related to libraries with Keener. Moreover, Gariepy describes libraries in which mutations are introduced into the binding domain (*i.e.*, the ***B chain***) of protein toxins, not the A chain. Thus, Gariepy teaches away from introducing inserts into the protease sensitive loop of the ***A chain*** of ABx toxic proteins.

For at least the above reasons, neither Keener nor Gariepy, either alone or in combination, renders amended claim 1 (and thus, claims dependent therefrom) obvious. Accordingly, applicants request that the Examiner withdraw the rejection.

CONCLUSION

Applicants respectfully request favorable consideration of the application and early allowance of the pending claims.

Respectfully submitted,

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